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1.	Your reference	4-33300P1
2.	Patent application number *(The Patent Office will fill in this part)*	0319497.4
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)* Patent ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND 07125487005 SWITZERLAND
4.	Title of invention	Organic compounds
5.	Name of your agent *(If you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)*	Craig McLean Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB 07181522002 ✓
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Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application

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Mrs. S. Schnerr 01403 323069

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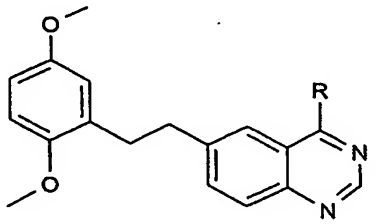
Organic Compounds

This invention relates to topical pharmaceutical compositions, e.g. in form of an emulsion, comprising a lavendustin of formula (I).

The present invention in particular provides topical pharmaceutical compositions comprising a lavendustin of formula (I) or a pharmaceutically acceptable salt thereof. The compounds of formula (I) have been disclosed e.g. as example 6 (hereinafter compound A), example 16 (hereinafter compound B), and example 17 (hereinafter compound C) in US 5,990,116, the contents of which are incorporated by reference. Preferred is 6-[2-(2,5-dimethoxyphenyl)-ethyl]-4-ethyl-quinazoline (compound A).



(I)

R = CH_2CH_3, OCH_3, CH_3

These compounds are useful in the topical treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrhoic keratosis, and skin cancer. Hyper-proliferative skin disorders are often accompanied by a hyperkeratosis. In particular, actinic keratosis is a skin disease with horny and dry skin lesions.

Treatment of hyperproliferative disorders can include destructive methods (cryotherapy, electro-desiccation and curettage, excisional therapy) and topical chemotherapy. Destructive methods and surgery may cause pain, blistering, scars and pigment changes and therefore, especially for patients with multiple lesions, topical chemotherapy is preferred.

Little is known about the mechanism of action of lavendustins, e.g. of formula (I), but like other antiproliferative agents, they may cause skin irritation. A composition of 0.5% of lavendustin of formula (I) for example in ethanol/water showed a severe skin irritation potential as demonstrated in an in vitro human epidermis model.

Applicants have found that compositions comprising a lavendustin, e.g. those of formula (I), and an emollient may be formulated into compositions of good physico-chemical stability, have good penetration and good tolerability and allow application on skin, e.g. face, and mucous membranes.

Accordingly the invention provides in one aspect, a topical composition comprising a lavendustin, e.g. of formula (I), and an emollient.

Suitable emollients may be selected, e.g. from

i) liquid fatty alcohols, saturated and/or unsaturated, branched and/or unbranched, having e.g. a C_8 to C_{24} chain. Prefered is oleyl alcohol, e.g. as known and commercially available under the trade name HD Eutanol® from e.g. Henkel, Germany;

ii) liquid waxes, e.g. natural-, synthetic-, semisynthetic- or emulsifying- waxes. Preferably isopropyl myristate, e.g. as known and commercially available from Henkel, Germany; oleyl erucate, e.g. as known and commercially available under the trade name Cetiol® J600 from e.g. Henkel, Germany; diisopropyl adipate, e.g. as known and commercially available under the trade name Isopat® 1794 from e.g. Dargoco, Germany; and/or oleyl oleate, e.g. as known and commercially available under the trade name Cetiol® from e.g. Henkel, Germany;

iii) di- and tri- glycerides, having e.g. C_8 to C_{24} fatty acids, e.g. a medium chain fatty acid triglyceride, e.g. Miglyol®812. Miglyol®812 is a fractionated coconut oil comprising caprylic-capric acid triglycerides and having a molecular weight of about 520 daltons. Fatty acid composition = C_6 max. about 3%, C_8 about 50 to 65%, C_{10} about 30 to 45%, C_{12} max 5%; acid value about 0.1; saponification value about 330 to 345; iodine value max 1. Miglyol® 812 is commercially available from e.g. Hüls Chemie AG, Germany;

iv) propylene glycol mono- and di- fatty acid esters such as propylene glycol caprylate commercially available under the trade name Miglyol® 840 (Fiedler, loc. cit., p. 1009), propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycolricinoleate, and propylene glycol stearate;

v) petrolatum, e.g. white petrolatum, e.g. as known and commercially available from e.g. Mineral Chemie AG, Germany; and

vi) mixtures of any of components i) to v).

The lavendustin is present in the compositions of the present invention in an amount of from 0.01 to 10%, e.g. from 0.05 to 3%, e.g. from 0.1 to 2%, e.g. from 0.2 to 1%, e.g. 0.8% by weight based on the total weight of the composition.

The emollient may be present in an amount of about 5 to about 40%, preferably 5 to 30% by weight based on the total weight of the composition.

The compositions of the present invention are preferably in form of emulsions, even more preferably in form of oil-in-water emulsions. Accordingly, this invention further provides a topical composition in form of an emulsion, e.g. in form of an oil-in-water emulsion, comprising a lavendustin, e.g. of formula (I), and an emollient.

Preferably, the lavendustin, e.g. of formula (I), or a pharmaceutically acceptable salt thereof is dissolved in the lipophilic components, such as the emollients, and is released from the formulation in a uniform and sustained way thereby avoiding high local concentrations, i.e. which could cause irritation, of the lavendustin in the skin or mucous membrane.

In another aspect, the present invention provides compositions comprising lavendustin, e.g. of formula (I), or a pharmaceutically acceptable salt thereof which avoid high local concentration of the lavendustin in the skin or mucous membrane.

The composition of the present invention may further comprise hydrophilic components such as propylene glycol, hexylene glycol, liquid polyethylene glycol such as PEG 200, 300, 400 or 600, and/or glycerol. The hydrophilic components may be present in amounts of about 1 to up to about 20%, e.g. from about 1 to about 5% by weight based on the total weight of the composition.

The composition of the present invention may further comprise water, e.g. purified water. Water may be present in amounts of about 20 to up to about 90%, e.g. from about 35 to about 80% by weight based on the total weight of the composition.

The compositions of the present invention may further comprise emulsifiers. Such emulsifiers are described in standard texts such as Fiedler, H.P.; 1996; Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; Editio Cantor Verlag Aulendorf (Germany), and Kibbe, A.H.; 2000; Handbook of Pharmaceutical Excipients, a joint publication of Pharmaceutical Press, London (UK), and American Pharmaceutical Association, Washington (US). Examples of suitable emulsifiers include:

i) sorbitan fatty acid esters, e.g. sorbitan mono C_{12-18} fatty acid esters, sorbitan sesqui C_{12-18} fatty acid esters or sorbitan tri C_{12-18} fatty acid esters as known and commercially available under the trade mark Span® or Arlacel®. Particularly preferred are the products Span® 20, a sorbitan monolaurate, having a D^{25} of about 1, a HLB of about 8.6, a viscosity of about 3900 to 4900 mPa·s, or Arlacel® 83, a sorbitan monosesquioleate, having a D^{25} of about 1, a HLB of about 3.7, a viscosity of about 1500 mPa·s, or Span ® 60, a sorbitan monostearate, having a HLB of about 4.7, an acid value of about 5 to 10 (Fiedler, loc. cit., p. 1426; Handbook of Pharmaceutical Excipients, loc. cit., page 511);

ii) polyoxyethylene-sorbitan-fatty acid esters, for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type, also called polysorbates, known and commercially available under the trade name Tween® (Fiedler, loc. cit. p.1615; Handbook of Pharmaceutical Excipients, loc. cit., page 416), including the products Tween®
20 [polyoxyethylene(20)sorbitanmonolaurate],
21 [polyoxyethylene(4)sorbitanmonolaurate],
40 [polyoxyethylene(20)sorbitanmonopalmitate],
60 [polyoxyethylene(20)sorbitanmonostearate],
65 [polyoxyethylene(20)sorbitantristearate],
80 [polyoxyethylene(20)sorbitanmonooleate],
81 [polyoxyethylene(5)sorbitanmonooleate],
85 [polyoxyethylene(20)sorbitantrioleate].
Especially preferred products of this class are Tween® 20 and Tween® 60;

iii) salts of fatty alcohol sulfates such as sodium lauryl sulfate and sodium cetylstearyl sulfate, preferably sodium cetylstearyl sulfate as known and commercially available under the trade name Lanette® E (Fiedler, loc. cit., p. 892) from Henkel, Germany; and

iv) polyoxyethylene alkyl ethers, e.g. polyoxyethylene glycol ethers of C_{12} to C_{18} alcohols, e.g. polyoxyethylene cetyl ether or polyoxyethylene oleyl ether, or polyoxyethylene stearyl ether, as known and commercially available under the trade name Brij® (Fiedler,

loc. cit., p. 259; Handbook of Pharmaceutical Excipients, loc. cit., page 407);

v) polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj® (Fiedler, loc. cit., p. 1042; Handbook of Pharmaceutical Excipients, loc. cit., page 420). An especially preferred product of this class is e.g. Myrj® 52, a Polyoxyethylene 40 stearate having D^{25} of about 1.1, a melting point of about 40 to 44°C, a HLB value of about 16.9., an acid value of about 0 to 1 and a saponification no. of about 25 to 35;

vi) polyoxyethylene-polyoxypropylene copolymers and block co-polymers such as those known and commercially available under the trade names Pluronic®, Emkalyx®, and Poloxamer® (Fiedler, loc. cit., p. 1200, 1203; Handbook of Pharmaceutical Excipients, loc. cit., page 386) and in particular Poloxamer® 188 and Pluronic® F68, having a D^{25} of about 1.1, a melting point of about 40 to 44°C, and a HLB value of about 16.9;

vii) esters of polyethylene-glycol glycerol ethers that have at least one free hydroxyl group and aliphatic C_8-C_{22} carboxylic acids. Examples include PEG-20 glycerine mono stearate;

viii) reaction products of a natural or hydrogenated castor oil and ethylene oxide. The polyethyleneglycol hydrogenated castor oils are available under the trade name Cremophor® (Fiedler, loc. cit., p. 392). Particularly suitable are Cremophor® RH 40, having a saponification value of about 50 to 60, an acid value less than about 1, a water content (Fischer) less than about 2%, a n_D^{60} of about 1.453 to 1.457 and a HLB of about 14 to 16; Cremophor® RH 60, having a saponification value of about 40 to 50, an acid value less than about 1, an iodine value of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, a n_D^{25} of about 1.453 to 1.457 and a HLB of about 15 to 17, and Cremophor® EL, having a molecular weight (by steam osmometry) of about 1630, a saponification value of about 65 to 70, an acid value of about 2, an iodine value of about 28 to 32 and a n_D^{25} of about 1.471. Also suitable are various tensides available under the trade names Nikkol® (Fiedler, loc. cit., p. 1087), Emulgin® (Fiedler, loc. cit., p. 545), Mapeg® (Fiedler, loc. cit., p. 967) and Incrocas® (Fiedler, loc. cit., p. 800);

ix) polyoxyethylene glyceride as commercially available under the trade name Labrafil® (Fiedler, loc. cit., p. 880), particularly Labrafil® M2130 CS;

x) glycerine sorbitan fatty acid esters as commercially available under the tradename Arlacel ® 481 having a molecular weight of about 630, a HLB value of about 4.5 (Fiedler, loc. cit., p. 192);

xi) mixtures of any of components i) to x).

It is to be appreciated that emulsifiers may be complex mixtures containing side products or unreacted starting products involved in the preparation thereof, e.g. emulsifiers made by polyoxyethylation may contain another side product, e.g. polyethylene glycol.

If the composition is a water-in-oil emulsion, the emulsifier selected preferably has a HLB value of 10 to 15. If the emulsion is an oil-in-water emulsion, the emulsifier selected has a HLB value of 4 to 8. A combination of emulsifiers having different HLB values may be used to achieve a desired HLB value. Preferably the emulsifiers are present in an amount of about 1 to about 30% weight based on the total weight of the composition, and more preferably 10 to 25%.

Preferably, the compositions are in form of e.g. a cream, a lotion or an emulsion gel.

If desired, the compositions of the invention may comprise consistency agents, preferably a mixture of consistency agents. Suitable consistency agents include e.g.

i) solid alcohols, having e.g. a C_{12} to C_{24} chain, e.g. cetyl alcohol and/or stearyl alcohol. Cetyl alcohol and stearyl alcohol may be commercially available e.g. under the trade names Lorol® C16 and Lorol® C18, respectively, from Henkel, Germany;

ii) esterified compounds of fatty acid and fatty alcohols. They may include esterified compounds of fatty acid having e.g. a C_{12} to C_{24} chain, saturated or unsaturated, and primary alcohol having e.g. a C_{12} to C_{24} chain, e.g. cetyl palmitate as commercially available under the trade name Cutina® CP from Henkel, Germany;

iii) glycerine monostearate known and commercially available under the trade mark Imwitor® (Fiedler, loc. cit., p. 799; Handbook of Pharmaceutical Excipients, loc. cit., page 225), particularly Imwitor 960;

iv) solid fatty acids, having e.g. a C_{12} to C_{24} chain, e.g. stearic acid and its salts, e.g. aluminium- or magnesium stearate;

v) solid waxes, e.g. bees wax or carnauba wax;

vi) mixtures of any of components i) to v).

Consistency agents are preferably present in an amount of from about 1 to about 30%, e.g. from about 4 to about 10% by weight based on the total weight of the composition.

If desired, the compositions of the invention may comprise gelling agents. Suitable gelling agents include carbomers e.g. crosslinked poly(acrylic acid) polymers such as known and commercially available under the trade name Carbopol® (Fiedler, loc. cit., p. 301; Handbook of Pharmaceutical Excipients, loc. cit., page 79). Carbopol® 974P and Carpopol® 1342 are preferred. The gelling agents are preferably present in an amount of 0.2 to 2%, more preferably less than about 1% by weight based on the total weight of the composition.

The compositions may further comprise preserving agents, e.g. microorganism growth inhibitors, such as methyl- or propylparabene, phenyl alcohol, benzyl alcohol, propylene glycol, sorbic acid, and chlorcresol may be included as appropriate. Preserving agents are preferably present in an amount of about 0.05 to about 1% by weight based on the total weight of the composition.

The compositions may further comprise antioxidants such as butyl-hydroxytoluene, ascorbyl palmitate, sodium pyrosulfite, butyl-hydroxy anisole, propyl p-hydroxybenzoate, methyl p-hydroxybenzoate and tocopherol, as appropriate. Antioxidants are preferably present in an amount of about 0.01 to about 2.5% by weight based on the total weight of the composition.

If desired, pH modifying agents may be included to bring the pH of the composition to between 4 and 6 or by adding a pharmaceutically acceptable buffer system, e.g. by addition of solution (10%) of sodium hydroxide. A pH of between 4 and 6 is desirable to avoid skin and mucous membrane irritation.

It will be appreciated that although the excipients have been described above by reference to a particular function, any particular excipient may have alternative or multiple functions, e.g. propylene glycol may act as e.g. hydrophilic component and/or preserving agent.

The compositions of the invention may be prepared in a conventional manner by dissolving the appropriate amount of lavendustin in the lipophilic components such as lipophilic carrier and consistency agent at elevated temperatures, e.g. at 60 to 80 °C, and adding the aqueous phase under stirring and homogenization. Further hydrophilic excipients like buffering agents, gelling agents and preservatives are added to the water phase. The emulsifiers may be added either to the lipophilic or hydrophilic components depending on their HLB values. After homogenization, the compositions are cooled to room temperature under stirring.

Accordingly, in another aspect the present invention provides a process for the preparation of a topical pharmaceutical composition, comprising dissolving the appropriate amount of a lavendustin, e.g. of formula (I), or a pharmaceutically acceptable salt thereof in the lipophilic components such as emollient and consistency agents, if present, at elevated temperatures, e.g. at 60 to 80 °C, and adding the water phase under stirring and homogenization.

The compositions according to the present invention are useful for the known indications of lavendustin, particularly in the treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrhoic keratosis, and skin cancer.

Therefore, in a further aspect the present invention provides a composition as defined above for use in the treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrhoic keratosis, and skin cancer.

In another aspect the present invention provides a method for treating hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrhoic keratosis, and skin cancer comprising administering a composition as defined above to the skin or mucous membrane of a patient in need thereof.

In yet another aspect the present invention provides the use of a composition as defined above in the preparation of a medicament for the treatment of hyperproliferative disorders such as actinic keratosis, anogenital warts and seborrhoic keratosis, and skin cancer.

The utility of the topical compositions according to the invention may be observed in standard clinical tests. A representative clinical trial may be carried out as follows:
A randomised single-centre, double-blind, within-subject vehicle-controlled study of a composition of the present invention at a dose of 0.1 to 2 % active agent by weight based on the total weight of the composition over e.g. 10 cm^2, corresponding to a dose of about 0.1 to 1 mg/cm^2, is performed in subjects with actinic keratosis, anogenital warts and seborrhoic keratosis, and skin cancer.
In total 15 to 36 subjects are treated with the composition once or twice daily for up to two weeks. The therapeutic effect on erythema, edema, pruritus, burning/stinging/pain, erosion is evaluated separately for each treated lesion. Local tolerability and cosmetic outcome of

each treatment and routine safety parameters, including hematology and blood chemistry, are assessed.

The compositions of the present invention are found to be effective.

The exact amount of lavendustin and of the composition to be administered depends on several factors, for example the desired duration of treatment and the rate of release of the active agent. Satisfactory results are obtained in larger mammals, e.g. humans, with the local application over the area to be treated of a 0.01 to 10% by weight based on the total weight of the composition, e.g. 0.05 to 3%, preferably 0.1 to 2%, more preferably 0.2 to 1%, most preferably 0.8%, concentration of the lavendustin once or several times a day (for example 1 to 5 times a day). In general, the compositions may be applied to areas of skin and mucous membranes as small as 1 cm^2 to as large as 1 m^2. Suitable skin and mucous membrane loadings fall within the range of 0.1 mg/cm^2 to 10 mg/cm^2, e.g. 2 mg/cm^2, of lavendustin composition.

Following is a description by way of example only of compositions of this invention.

Examples 1 to 6

The formulations of example 1 to 6 as shown in *Table 1* showed good physico-chemical stability, and are mild to moderate irritants as determined *in vitro* by using a human epidermis model.

Example 7:

In vitro penetration of compound A of examples 1 to 4 into stripped epidermal layer of human skin was good; concentration of compound A in skin was between 0.4 and 1.3 $\mu g/cm^2$ (calf serum/PBS 1:2 (vol:vol); pH = 7.4).

Example 8:

In total 36 subjects with actinic keratosis were treated once or twice daily over up to two weeks with the composition of example 4. The formulation of example 4 was effective. Local tolerability and cosmetic outcome were good. Adverse events were minor. Plasma levels of compound A were low, ranging from 0.034 to 3.3 ng/ml.

Table 1

Component [in g]	Ex.1	Ex.2	Ex.3	Ex.4	Ex.5	Ex.6
Compound A	3	1	0.8	1	0.8	0.5
oleyl alcohol	10	-	-	-	-	-
medium chain fatty acid triglyceride	14	-	-	-	-	7.5
isopropyl myristate	-	10	10	9	12	-
petrolatum white	-	4	15	-	-	25
glycerine	-	-	5	-	-	-
propylene glycol	5	5	-	-	5	10
sorbitan monostearate	-	-	-	1.9	1.9	-
sorbitan sesquioleate	-	1	-	-	-	-
polyoxyethylene(20)sorbitanmonolaurate	-	-	2	-	-	-
polyoxyethylene(20)sorbitanmonostearate	-	3	-	6.1	6.1	7
glycerol monostearate	2	2	-	-	-	4
sodium cetylstearyl sulfate	1	-	-	-	-	-
cetyl alcohol	4	-	5	4	4	6
stearyl alcohol	4	12	5	4	4	-
cetyl palmitate	-	3	-	-	2	-
benzyl alcohol	-	-	-	-	1	-
water, purified	to 100	to 100	to 100	to 100	to 100	to 100

Examples 9 to 11

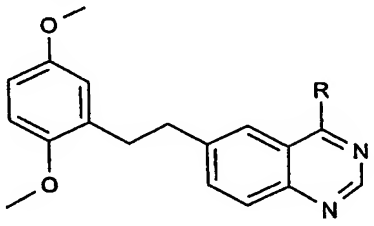
An oil-in-water cream emulsion is prepared in conventional manner having the following composition:

Component [in g]	Ex.9	Ex.10	Ex.11
Compound A	0.2	0.6	1.0
isopropyl myristate (emollient)	8.0	8.0	8.0
polysorbate Tween 60^{R} (emulsifier)	6.0	6.0	6.0
sorbitan monostearate (Span 60^{R}) (emulsifier)	2.0	2.0	2.0
cetyl alcohol (consistency agent)	4.0	4.0	4.0
stearyl alcohol (consistency agent)	4.0	4.0	4.0
cetyl palmitate (consistency agent)	2.0	2.0	2.0
benzyl alcohol (preserving agent)	1.0	1.0	1.0
water, purified	to 100	to 100	to 100

In examples 1 to 6 and 9 to 11 compound A may be replaced with compound B or compound C.

Claims

1. A topical pharmaceutical composition comprising a lavendustin of formula (I) or a pharmaceutically acceptable salt thereof and an emollient.



(I)

$R = CH_2CH_3$, OCH_3, CH_3

2. A composition according to claim 1 wherein the emollient comprises isopropyl myristate.

3. A composition according to claim 1 or 2 in form of an emulsion, e.g. in form of an oil-in-water emulsion.

4. A topical pharmaceutical composition comprising a lavendustin of formula (I) or a pharmaceutically acceptable salt thereof which avoids high local concentration of the lavendustin in the skin or mucous membrane.

Abstract

Organic Compounds

This invention relates to topical pharmaceutical compositions, e.g. in form of an emulsion, comprising a lavendustin or a pharmaceutically acceptable salt thereof and an emollient.